REMARKS

I. Preliminary Remarks

Applicants acknowledge with thanks the Examiner's decision to withdraw numerous aspects of the Restriction Requirement as set forth at pages 2-3 of the Office Action. Likewise, the withdrawal of numerous prior rejections is acknowledged with thanks.

The Examiner objected to the title of the application because it is not descriptive of the claimed invention. The title of the application is amended to herein to "Assays for Beta-Secretase Activity." The Examiner also objected to the typographical error in claim 130, which is corrected by the foregoing amendment. Various other typographical errors are also corrected by the foregoing amendment. These amendments do not add new matter to the application. Applicants request that the objections to the claims and specification be withdrawn in view of the foregoing amendments.

II. The rejection under 35 U.S.C. § 112, second paragraph should be withdrawn.

The Examiner rejected claims 102-131 under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter regarded as the invention. The Applicants traverse this rejection.

In particular, the Examiner asserted that claim 102 is indefinite for reciting the phase "wherein a human aspartyl protease encoded by the nucleic acid sequence of SEQ ID NO: 1 or SEQ ID NO: 3 cleaves said peptide between P1 and P1'." The claim specifies that the substrates recited in the claim be of a structure that is cleaved between P_1 and $P_{1'}$ by the specified human aspartyl protease. In the words of the Examiner, this phrase recites a physiochemical property or function of the substrates used in the methods of the invention. The physiochemical property at issue is equivalent to "activity" and can be assayed in exactly the same manner used to measure human aspartyl protease activity, *e.g.* a protease contacts a substrate and cleavage of the substrate by the protease is observed or measured.[1] The physiochemical properties of the enzyme and the substrate together determine whether

[1] The Examiner suggested a new recitation of activity such as "wherein $P_2P_1P_{1'}P_{2'}$ has [a certain] Hu-Asp2 activity." This suggestion was not adopted. The formula of $P_2P_1P_{1'}P_{2'}$ does not have Hu-Asp2 activity, because it defines the substrate for Hu-Asp2 and not the enzyme itself.

cleavage occurs. To further clarify that the phrase in question describes a property of a molecule rather than "a positive, proactive method step," the Applicants have amended the second wherein clause to be in passive tense rather than active tense. Amended claim 102 is intended to have equivalent scope and meaning as the original active claim.

In addition, the Examiner alleged that the exclusionary limitation in claim 102 ("does not comprise") is indefinite because it is unclear what sequences fall within the scope of the claim. As the Examiner apparently recognized, the sequences recited in claim 102 are set out in Table 1 (pages 17-19) and the depicted hyphen indicates the putative cleavage site of the peptide. In addition, the specification teaches that the scissile bond is between the P_1 and $P_{1'}$ residues of the peptide substrate. (*See* page 19, lines 5-7). Thus, one of skill in the art can clearly deduce the identity of the P_2P_1-$P_{1'}P_{2'}$ of the sequences recited in claim 102. The claim is unambiguously interpreted with reference to the specification, so the rejection should be withdrawn. [2]

The Examiner also stated that dependent claim 131 is indefinite because the limitation of the "protease" is broader than the protease encompassed by claim 102. Applicants traverse this rejection because the sequence limitation of claim 131 further limits the polypeptide limitation of claim 102, which requires that the polypeptide have β-secretase APP processing activity. However, claim 131 is amended herein to recite "the polypeptide" rather than "the protease," which should clarify the claim by improving antecedent basis.

In view of the foregoing amendment and remarks claims 102-131 are clear and definite. Applicants request that the rejections under 35 U.S.C. § 112, second paragraph, be withdrawn.

III. The rejection under 35 U.S.C. 112, first paragraph should be withdrawn.

The Examiner rejected claims 102-109 and 117-131 under 35 U.S.C. 112, first paragraph for lack of adequate written description. The Examiner asserted that the state of the art suggests that the Applicants were not in possession of the claimed invention and have

[2] At the Examiner's request, Applicants could import the $P_2P_1P_{1'}P_2$ explanation into the sequence listing itself, in a comment field for each sequence, but the amendment to the sequence listing would be redundant to Table 1, which already contains cross-references to the sequence listing.

not provided a sufficient description to support the broad genus recited in the claims. The focus of the rejection is the genus of substrate molecules defined by the claims. The Applicants traverse this rejection.

According to the United States Patent and Trademark Office Revised Interim Written Description Guidelines, the specification provides an adequate written description of a genus if a representative number of species are implicitly or explicitly disclosed. What constitutes a "representative number of species" is determined by what one of skill in the art would recognize as possession of the necessary common attributes or features of the elements possessed by the members of the genus in view of the species disclosed or claimed (see page 9 of Written Description Guidelines, 66 Fed. Reg. 1099, 2001).

A. Analysis of the claimed subject matter and descriptive support in the application.

At the outset, it is important to fairly characterize the scope of the genus that is at issue in the application. The claims recite a peptide substrate of at least six amino acids, which, without more, represents a finite number of peptide sequences.[3] However, the genus of 6-mer peptides in the claims actually is orders of magnitude narrower than the genus of all possible 6-mer peptides, because at least four (claim 102) to as many as six of the six residues defining the protease cleavage site are further restricted in the claims by "Markush" style groups of amino acids. While the genus may seem large in some contexts, it is a pittance in the fields of chemistry and molecular biology, where automated synthesis techniques, recombinant techniques, and high throughput screening techniques (to name just a few) abound, making manipulation and testing of large numbers of molecules a common occurrence. In view of the guidance in the specification and the known properties of conservative amino acid substitutions, the total number of possible species is less than what the Patent and Trademark Office routinely issues in connection with an allowance of a typical genus claim in a specification directed to traditional organic chemical pharmaceuticals. The written description training materials approve of this practice, *e.g.*, by approving of claims to a genus of biomolecules by "percent identity" to a reference sequence, together with a limitation of function.

The claims read on substrates that are longer than 6 amino acids. However, the applicants teach in the application (as recognized by the Examiner) and nicely explained in their later-published paper by Tomasselli *et al.* that additional amino acids appears to enhance the reactivity of β-secretase toward the recognition site. (*See* Tomasselli at p. 1009 and Table 1, for example.)

The present application also teaches activity assays that can be used to select from the genus of peptides satisfying the structural limitations of the claims only those peptides which also satisfy the functional limitations of the claims, namely, that the peptide is cleaved by an enzyme of interest (β-secretase). Through the combination of structural and functional limitations, the claims read only on "active" (cleavable) substrates. Through the teachings of assays, the application permits identification of the cleavable substrates through nothing more than routine screening.

In addition, the specification exemplifies 48 species that are encompassed by the claimed genus (see page 20, lines 5-14, page 21, lines 12-22, page 24, lines 3-10, page 25, lines 1-14, page 26, lines 3-25). The specification provides data to demonstrate that 26 of the disclosed species are cleaved between the P_1 and $P_{1'}$ residues by a human aspartyl protease. Further, the specification provides a number of exemplary species based on the teachings in Table 6 (page 303, lines 5-15). The specification also teaches one of skill in the art how to test any possible species for cleavage by a human aspartyl protease. (*See, e.g.*, page 79, lines 30 through page 81, line 14). The disclosed species, which vary in amino acid sequence and length, the disclosed formula to generate species that possess the structural requirements of the genus and the teaching of screening assays to measure aspartyl protease cleavage of any substrate demonstrate that the Applicants were in possession of the claimed genus at the time of filing.

B. Response to Specific Points Raised by the Examiner

In the Office Action, the Examiner cited teachings in the art to support his statement that one of skill in the art would doubt that Applicants had adequately described the invention as broadly claimed. However, these documents, which were published after the filing date of the present application, illustrate that one of skill in the art understands the

[3] See also Table 6 in the specification, which provides preferred residues for positions surrounding the

necessary common attributes or features of the elements possessed by the members of the genus. For example, Gruninger-Leitch *et al.* (*J. Biol. Chem.* 277: 4687-4693, 2002) provides 7 modified or artificial APP β-secretase cleavage sites that were cleaved by a human aspartyl protease. In addition, Shi *et al.* (*J. Alzheimer's Disease* 7: 139-148, 2005) tested the activity of 24 mutate APP substrates and all but one were cleaved by β-secretase.

In particular, the Examiner pointed to Table 1 of Gruninger-Leitch *et al.* to illustrate that a single change to the amino acid sequence of a substrate may result in a decrease in cleavage activity. However, all substrates set out in Table 1 of Gruninger-Leitch *et al.* that were designed to be cleaved by the β-secretase enzyme, exhibited some activity. The inactive substrates were either designed to be cleaved by α-secretase or renin, and these substrates are not encompassed by the genus of peptides encompassed by claim 102. Further, the substrates encompassed by the pending claims are required to be cleaved by a human aspartyl protease. This raises two important points. First, the claims exclude all inoperable embodiments. Second, all of the substrates for use in the claimed methods are cleaved at a useful rate. However, it is unfair to assert that substrates cleaved at a lower efficiency do not support the claimed genus when this measured efficiency was determined by a comparison of cleavage of the highly efficient "Swedish mutation" substrate. Even the wild-type substrate has only 9% cleavage compared to the Swedish mutation, yet it can be used in assays. These cited documents further support the claimed genus with observations such as, "[t]he data presented above also indicates that BACE can accept a wide variety of peptidic substrate." (Gruninger-Leitch *et al.* page 4692, bottom of right column.) and "[t]he results of the present investigation further indicate that BACE1 can accept a wide variety of amino acid residues at the β-scissile-bond of its substrate both in vitro and in cells." (Shi *et al.* page 146, left column).

The Examiner cited two Federal Circuit decisions (*Regents of University of California v. Eli Lilly & Co.*, 119 F.3d 1159, 43 USPQ2d 1398 (Fed. Circ. 1997); denoted at "*Lilly*" and *Enzo Biochem, Inc. v. Gen-Probe Inc.*, 285 F.2d 956, 63 USPQ2d 1609 (Fed. Circ. 2002) denoted as "*Enzo*") to support the position that to adequately support a broad genus the written description in the specification must set forth the common features

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cleavage site.

possessed by members of the genus and must describe a sufficient number of species within the genus. As described above, the specification has provided a representative number of species and these cases are distinguishable from the present application.

In *Lilly,* the disclosure in the patent at issue provided the cDNA sequence encoding a rat insulin protein. The claims were broadly directed to a cDNA sequence encoding a vertebrate insulin protein, a mammalian insulin protein and a human insulin protein without disclosure of the nucleotide sequences for the other, naturally occurring species. The "generic" limitation in the claims and supporting description in the present specification provide the structural features common to all species encompassed by the claimed genus by providing a formula for all possible species in Table 6 (page 30). The present application is more analogous to a claimed genus case than a naturally occurring biological variant case. The specification further provides numerous examples of particular substrate sequences in addition to a number of species that were actually shown to be cleaved by a human aspartyl protease. Thus, the present specification provide the structural features commonly possessed by members of the genus that distinguish them from others as required by the holding in *Lilly.*

In *Enzo,* the patent at issue disclosed probes that selectively hybridized to publicly deposited stains of *N. gonorrhoeae* and did not hybridize to *N. meningitides.* The probes in *Enzo* were described in the specification by their biological function and by reference to the deposited strains rather than by nucleotide sequence. The claimed genus of the present invention is defined by physiochemical property (cleavage between the P_1 and $P_{1'}$ residues by a human aspartyl protease), and the structural sequence is provided by the formula set out in Table 6 (page 30). The holding in *Enzo* states the standard for determining what is a representative number of species for the claimed genus is whether one of skill would find the generically claimed sequences described in the specification. Here, a chemical formula defines the structure of the genus. The state of the art and specifically teachings of 48 species in the specification further support a conclusion that the claimed genus is adequately described, and that the holding by the Federal Circuit in *Enzo* is easily distinguished on its facts.

Even though the examiner cited "written description" cases that concerned themselves with the inappropriateness of claiming solely by function, and not by structure, the examiner did not and cannot reasonably analogize the present case to such decisions. Rather, the Examiner focuses on alleged unpredictability of the changing of amino acid residues on the suitability of a sequence as a β-secretase substrate. Such analysis is more typically reserved for questions of enablement, and such questions have already been resolved in the Applicant's favor. The claiming of a limited genus, and the teachings of how to make peptides and evaluate their suitability as substrates with routine screening assays, and the providing of working examples, indicate that the claims are enabled. Moreover, the claims are limited by functional language so as only to encompass working embodiments. Even if the claims did read on inoperative embodiments, the law says that there is no requirement that every possible substrate amino acid sequence encompassed by the claimed genus be operable. It is the not the function of the claims to specifically exclude possible inoperative substrates and undue experimentation depends on whether the number of inoperative substrates becomes significant. *Atlas Powder Co. v. E.I. Du Pont de Nemours & Co. and Alamo Explosives Co. Inc.* 750 F.2d 1569, 1576 (Federal Circuit 1984).

In view of the foregoing remarks, claims 102-109 and 117-131 are adequately described in the specification. Applicants request that the rejection under 35 U.S.C. § 112, first paragraph for lack of written description be withdrawn.

IV. The Rejections under 35 U.S.C. § 102(e) should be Withdrawn

The Examiner rejected claims 102-115, 117-121 and 123-131 under 35 U.S.C. § 102(e) as allegedly being anticipated by Fang *et al.*, U.S. Patent Application Publication No. 2003-0096864 A1 filed on June 29, 2001, which claims benefit of U.S. Provisional Application No. 60/215,323, filed June 30, 2000. In particular, the Examiner stated Fang *et al.* discloses a synthetic APP substrate having the amino acid sequence: GLNKTEEISEISY-EVEFRC (SEQ ID NO: 191 of the present application) that can be cleaved by β-secretase. The Applicants traverse this rejection.

For the purposes of the subject matter claimed in the present application, Fang *et al.* is not entitled to the benefit of the priority date of June 30, 2000, because the substrate

having amino acid sequence GLNKTEEISEISY-EVEFRC is not disclosed in the earliest filed application. The present application claims priority benefit of U.S. Provisional Application Nos. 60/219,795 and 60/275,251, filed July 19, 2000 and March 12, 2001, respectively. The effective priority date of the present application is before the filing date of the Fang *et al.* publication which discloses the substrate. Therefore, the pending claims are not inherently or literally anticipated by the disclosure in Fang *et al.* Applicants request that the rejection under 35 U.S.C. § 102(e) be withdrawn. [4]

V. The Rejection under 35 U.S.C. 103(a) should be Withdrawn

The Examiner rejected claims 102-115 and 117-131 under 35 U.S.C. § 103(a) as being obvious in view of Fang *et al.* (U.S. Application No. 2003-0096864 A1) and Zhang *et al.* (U.S. Patent No. 6,248,904). As stated above, Fang *et al.* is not entitled to its earliest priority date and therefore is not effective prior art, and Zhang *et al.* alone does not render the pending claims obvious. Applicants request that the rejection under 35 U.S.C. § 103(a) be withdrawn.

[4]Applicants reserve the right to demonstrate that, to the extent the cited reference discloses the invention of the present application, it was the disclosure of the Applicants' own work, and not the disclosure of the work of "another" as that term is used in 35 C.F.R. § 102(e).

CONCLUSION

In view of the above amendment and remarks, Applicants believe pending claims 102-131 are in condition for allowance and early notice thereof is requested. If further discussion would expedite allowance of the claims, the undersigned can be contacted at the number below.

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Respectfully submitted,

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